Remarks/Arguments

Reconsideration of the above-identified application in view of the present amendment is respectfully requested. By the present amendment, claim 17 has been amended to include a comma after the word oligonucleotide and claim 25 has been amended to recite that the growth factor or neurotrophic factor is administered to the subject. Below is a discussion of the objection to claim 17 and the 35 USC 103(a) rejection of claims 1, 12-13, 17 and 23-27.

Claim Objection

Claim 17 is objected to because it does not include a comma between oligonucleotides and ribosymes. Claim 17 has been amended to include a comma. Accordingly, withdrawal of the objection is respectfully requested.

35 USC 103(a) rejection of claims 1, 12-13, 17 and 23-25

Claims 1, 12-13, 17 and 23-25 are rejected under 35 USC 103(a) as being obvious over Fawcett et al. (Brain Research Bulletin, 199; 49(6): 377-391) in view of Kleesiek (WO 01/49831) and further in view of Jen et al. (Stem Cells 2000; 18: 307-319).

The Office Action argues that Fawcett et al. teach damage to the CNS results in the formation of glial scars (abstract) and chondroitin sulphate glycosaminoglycan (GAG) expression is increased around glial scars of CNS injury, GAG expression around glial scars inhibits axon growth, and disruption of proteoglycan synthesis has been shown to reduce inhibition of glial growth. The Office Action further argues that while Fawcett et al. do not teach using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs to inhibit XT-I or XT-II, Kleesiek teaches the cDNA of

XT-I and XT-II, that XT is initial step in the biosynthesis of the glycosaminoglycan linkage region, and making medicaments that are inhibitors of xylotransferase. The Office Action further argues that Kleesiek does not teach using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs to inhibit XT-I or XT-II but that Jen et al. teach designing antisense oligonucleotides, ribozymes and DNAxymes. The Office Action then argues it would be obvious to the skilled artisan to reduce GAG content in a glial scar to promote neuronal generation by inhibiting XT-I or XT-II using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs because the "use of antisense oligonucleotides are well known in the art to inhibit expression of genes by inhibiting mRNA", it seems possible to make a therapeutic inhibitor of XT-I and XT-II activity, and that all of the claimed elements were known in the prior art and one skilled in the art could have combined the claimed elements with no change in their respective function.

Claim 1 is not obvious over Fawcett et al. in view of Kleesiek and Jen et al. because: (1) Fawcett et al. in view of Kleesiek and Jen et al. do not teach or suggest to the skilled artisan that inhibiting expression or activity of XT-I and XT-II using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi can and/or will reduce glycosaminoglycan content in a glial scar of a mammal, (2) the Office Action provides no teaching or suggestion of administering the antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent intrathecally, topically, or locally to the glial scar; and (3) Fawcett et al. teach away from inhibiting expression or activity of XT-I and XT-II as a means to reduce glycosaminoglycan content in a glial scar of a mammal.

a. Fawcett et al. in view of Kleesiek and Jen et al. do not teach or suggest to the skilled artisan that inhibiting expression or activity of XT-I and XT-II using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi can and/or will reduce glycosaminoglycan content in a glial scar of a mammal.

Fawcett et al. as noted in the Office Action, do not teach or suggest using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs to inhibit XT-I or XT-II and that the inhibition of activity or expression of XT-I or XT-II will reduce glycosaminoglycan content in a glial scar of a mammal. In fact, Fawcett et al. do not teach inhibiting any enzyme with any type of inhibitor to reduce glycosaminoglycan count in a glial scar, let alone XT-I or XT-II. Fawcett et al. provide no information to suggest that they were even thinking of targeting XT. They only suggest targeting TGF-β with antibodies.

Kleesiek, likewise, does not teach or suggest using antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi constructs to inhibit XT-I or XT-II. Moreover, there is no teaching or suggestion in Kleesiek that administering antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi that inhibit expression of XT-I or XT-II will also reduce glycosaminoglycan content in a glial scar of a mammal.

Additionally, the Office Action has provided no evidence in fact that it was known at the time of the invention the glycosaminoglycan content of a glial scar of a mammal is directly or indirectly related to the expression and/or activity of XT-I or XT-II in a subject. As noted above, the Office Action merely states from Kleesiek that XT is an initial step enzyme in the biosynthesis of glycosaminoglycan. Kleesiek however notes that other enzymes are also involved in the production of

glycosaminoglycan. Specifically, Kleesiek teaches at page 3, lines 9+ that: "The biosynthesis of glycosaminoglycans requires the coordinated action of a large number of glycotransferases." Any of these other enzymes could potentially compensate for the lost function of XT. A skilled artisan in the field of neurobiology and microbiology would recognize that it is common for there to be functional redundancy in biological systems, such that other related proteins could potentially take over the role of XT *in vivo*. Examples of function redundancy of proteins are well known to one skilled in the art.

Kleesiek, therefore, do not teach that a glycosoaminoglycan reducing effect results from a lack of XT activity or expression. Given the well recognized complex role of glycoltransferases in the production of glycosaminoglycans in glial scars, without experiments to demonstrate that the inhibition of the expression or activity of XT is essential for reducing glycosaminoglycan content in glial scars, one skilled in the art cannot conclude that inhibiting the expression or activity of XT-I or XT-II will reduce glycosaminoglycan count in a glial scar of a mammal.

Additionally, at the time of the invention, the use of antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent for the *in vivo* treatment of mammals was unpredictable. The Office Action provides no evidence that at the time of the invention any scientists were using or testing antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent *in vivo* in the neurobiology field. Jen et al. merely teach that they had some success in tissue culture but "that effective and efficient clinical translation of the antisense strategy has proven elusive". (Page 315, column 2). Furthermore, antisense technology had and still has a reputation of being

unspecific and toxic. Accordingly, in contrast to the Office Action's assertion that Jen et al. make the use of any DNA enzyme or any antisense technology obvious, the skilled artisan would recognize that the use of DNA enzymes or antisense technology to inhibit expression or activity of XT-I or XT-II in a mammal is unpredictable and that it would not obvious to use antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi to XT-I or XT-II to reduce glycosaminoglycan content in a glial scar of a mammal particularly in view of Fawcett et al., Kleesiek, and Jen et al.

b. The Office Action provides not teach or suggestion of administering the antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent intrathecally, topically, or locally to the glial scar.

To establish a prima facie case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re* Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Fawcett et al. in view of Kleesiek and Jen et al. fail to teach or suggest administering the antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent intrathecally, topically, or locally to the glial scar as recited in claim 1. Moreover, the Office Action has failed to include any discussion or provide any teaching showing administration of antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent intrathecally, topically, or locally to the glial scar. Without such a teaching or suggestion, Fawcett et al. in view of Kleesiek and Jen et al. fail to teach all of the limitations of the claimed invention.

c. Fawcett et al. teach away from inhibiting expression or activity of XT-I and XT-II as means to reduce glycosaminoglycan content in a glial scar of a mammal.

Assuming arguendo that the prior art did suggest that inhibition of XT could potentially inhibit glycosaminoglycan synthesis, Fawcett et al. teach away from inhibiting expression or activity of XT-I and XT-II as a means to reduce glycosaminoglycan content in a glial scar of a mammal. Fawcett et al. state at the second paragraph, column 2, page 384 that:

> "Another potential strategy is to target proteoglycan synthesis in general, in the way that we have used in various in vitro models using chlorates and xylosides. However, this approach has problems: one is the toxic nature, diffusibility, and lack of specificity of the reagents, the other is that heparin sulphate proteoglycan synthesis is also affected, and these molecules are promoters of axon growth and necessary for various other functions. In order for this strategy to work it will be necessary to find a means of preventing the synthesis specifically of chondroitin sulfate GAGs."

Inhibition of expression or activity of XT-I and XT-II will reduce the production of all glycosaminoglycans in the glial scar including heparan sulphate, which Fawcett et al. teach promotes axon growth and is necessary for other functions. Attached herewith is an abstract of a recent publication from Applicants that shows administration of DNA enzymes to XT-I reduced chondroitin sulphate and heparan sulphate production. (Brain, 2008 131(10): 2596-2605, a copy of which is attached). Accordingly, a skilled artisan would not inhibit expression or activity of XT-I and XT-II as means to reduce glycosaminoglycan content in a glial scar because Fawcett et al. teach away from a non-specific glycosaminoglycan reducing method that would potentially reduce the production of promoters of axon growth, such as heparan sulphate.

Thus, Fawcett et al., in view of Kleesiek, and Jen et al. fail to teach all of limitations of claim 1, the skilled artisan would find the use antisense

oligonucleotides, ribozymes, DNA enzymes, or RNAi to XT-I or XT-II to reduce glycosaminoglycan content in a glial scar of a mammal unpredictable in view of Fawcett et al. Kleesiek, and Jen et al., and Fawcett et al. teach away from inhibiting expression or activity of XT-I and XT-II as means to reduce glycosaminoglycan content in a glial scar of a mammal. Therefore, withdrawal of the obviousness rejection of claim 1 is respectfully requested.

Claims 12 and 13 depend from claim 1 and are therefore patentable over Fawcett et al. in view of Kleesiek and Jen et al. because of the aforementioned deficiencies in the rejection with respect to claim 1 and the because the specific limitations recited in claims 12 and 13.

Claim 17 includes similar limitations as claim 1 and is therefore patentable over Fawcett et al. in view of Kleesiek and Jen et al. because of the aforementioned deficiencies in the rejection with respect to claim 1. Additionally, claim 17 is patentable over Fawcett et al. in view of Kleesiek and Jen et al. because the invention recited in claim 17 exhibits unexpected results.

The Court of Appeals for the Federal Circuit has stated that:

> An analysis of obviousness of a claimed combination must include consideration of the results achieved by the combination. Gillette Company *v.* S.C. Johnson & Sons, Inc., 919 F.2d 720, 16 USPQ2d 1923, (CAFC 1990)

This consideration must address objective evidence of nonobviousness. Graham v. John Deere Co., 383 US 1, 17-18, 148 USPQ 459, 467 (1966). This objective evidence can include a showing that claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would find surprising or unexpected. In re Mayne, 41 USPQ2d 1451, 1455, (CAFC, 1997).

Example 8 of the present application shows that:

> Our results indicated that XT-I DNA enzymes work *in vivo.* Administration of an XT-1 DNA enzyme decreases GAG content *in vivo.* Administration of an XT-I DNA enzyme also promotes neuronal regeneration *in vivo* following an injury to the spinal cord.
>
> A spinal cord injury was simulated in adult rats using a stab injury of the spinal cord at the C5-C6 level. The dura was opened at the C5-C6 level and a lesion was made by inserting a 25 gauge needle. Following injury, mouse dorsal root ganglia cells (DRGs) were transplanted in the C4-C5 region. The DRGs were derived from adult "green" mice. These mice express GFP under the control of the actin promoter, and thus the DRG cells are easily observable following transplantation. Following both injury and transplantation of DRG cells, animals were treated, at the cite of injury, with either an XT-I DNA enzyme or a control DNA enzyme. The enzyme was administered via an intratheca11y placed PE-l0 tubing connected to a P60 tubing filled with the DNA enzymes against XT-I. The tubing was connected to an osmotic minipump (Alzet). After 7 days of administration of the DNA enzyme, the animals were sacrificed and analyzed.
>
> Immunohistochemical analysis of sections through the spinal cord of these rats indicated decreased CS-56 staining in XT-I treated animals in comparison to control treated animals. Additional analysis of GFP expression demonstrated that transplanted DRG cells extended processes into and around the injury cite. Analysis of both CS-56 and GFP staining in the same section demonstrated that GAG content is decreased coincident to the regions where transplanted DRG cells migrate and extend neurites.

Moreover, the above-noted Brain 2008 abstract states:

> In the injured spinal cord, proteoglycans (PGs) within scar tissue obstruct axon growth through their glycosaminoglycan (GAG)-side chains. The formation of GAG-side chains (glycosylation) is catalysed by xylosyltransferase-1 (XT-1). Here, we knocked down XT-1 mRNA using a tailored deoxyribozyme (DNAXTas) and hypothesized that this would decrease the amount of glycosylated PGs and, consequently, promote axon growth in the adult rat spinal cord. A continuous 2-week delivery of DNAXT as near the rostral border of a peripheral nerve graft bridging the transected dorsal columns in the thoracic spinal cord resulted in an 81% decrease in XT-1 mRNA, an average of 1.4-fold reduction in GAG-side chains of chondroitin sulphate or heparan sulphate–PGs and 2.2-fold reduction in neurocan and brevican core

> proteins in scar tissue. Additionally, compared to control deoxyribozyme, the DNAXT as treatment resulted in a 9-fold increase in length and a 4-fold increase in density of ascending axons growing through the nerve graft and scar tissue present at the rostral spinal cord. Together our data showed that treatment with a deoxyribozyme against XT-1 mRNA decreased the amount of glycosylated PGs and promoted axon growth through scar tissue in the injured spinal cord. The deoxyribozyme approach may become a contributing factor in spinal cord repair strategies.

These results are unexpected in view of the teachings of the prior art which fail to show any evidence that inhibiting expression of XT-I can be used promote neuronal regeneration and especially in view of the teachings of Fawcett et al., which teach against promoting neuronal regeneration by non-specifically reducing glycosamionglycan production, such as heparan sulphate. Therefore, the present inventions exhibits unexpected results and allowance of claim 17 is respectfully requested.

Claims 23 and 24 depend from claim 17 and are therefore patentable over Fawcett et al. in view of Kleesiek and Jen et al. because of the aforementioned deficiencies in the rejection with respect to claim 17 and the because the specific limitations recited in claims 23 and 24.

Claim 25 depends from claim 17 and further recites that a growth factor or neurotrophic factor is administered.

Claim 25 is patentable over Fawcett et al. in view of Kleesiek and Jen et al. because of the aforementioned deficiencies in the rejection with respect to claim 17.

Additionally, claim 25 is patentable over Fawcett et al. in view of Kleesiek and Jen et al. because Fawcett et al. in view of Kleesiek and Jen et al. fail to teach or suggest the administration of a growth factor or a neurotrophic factor in combination

with administering the antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent intrathecally, topically, or locally to the glial scar.

To establish a prima facie case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re* Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Fawcett et al. in view of Kleesiek and Jen et al. fail to teach or suggest further administering a growth factor or a neurotrophic factor. Moreover, the Office Action has failed to include any discussion or provide any teaching showing further administration of a growth factor or a neurotrophic factor. Without such a teaching or suggestion, Fawcett et al. in view of Kleesiek and Jen et al. fail to teach all of the limitations of the claimed invention and withdrawal of the rejection of claim 25 is specifically requested.

Claims 26 and 27 depend from claim 25 and further specify the specific neutrophic factors and growth factors administered to the subject

Claims 26-27 are patentable over Fawcett et al. in view of Kleesiek and Jen et al. because of the aforementioned deficiencies in the rejection with respect to claim 25.

Additionally, claims 26 and 27 are patentable over Fawcett et al. in view of Kleesiek and Jen et al. because Fawcett et al. in view of Kleesiek and Jen et al. fail to teach or suggest the administration of the recited specific growth factors or neurotrophic factors in combination with administering the antisense oligonucleotides, ribozymes, DNA enzymes, or RNAi agent intrathecally, topically, or locally to the glial scar. Moreover, the Office Action has failed to include any discussion or provide any teaching showing further administration of the recited

growth factors or neurotrophic factors. Further, the Office Action has not even addressed these claims in its rejection. Absent some rejection of these claims, Applicants respectfully request that these claims be allowed.

In view of the foregoing, it is respectfully submitted that the present application is in a condition of allowance and allowance of the present application is respectfully requested.

Please charge any deficiency or credit any overpayment in the fees for this matter to our Deposit Account No. 20-0090.

Respectfully submitted,

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